



Robert Greene Sterne  
Edward J. Kessler  
Jorge A. Goldstein  
David K.S. Cornwell  
Robert W. Esmond  
Tracy-Gene G. Durkin  
Michele A. Cimbala  
Michael B. Ray  
Robert E. Sokohl  
Eric K. Steffe  
Michael Q. Lee  
Steven R. Ludwig  
John M. Covert  
Linda E. Alcorn  
Robert C. Millonig  
Lawrence B. Bugalsky  
Donald J. Featherstone  
Michael V. Messinger

Judith U. Kim  
Timothy J. Shea, Jr.  
Patrick E. Garrett  
Heidi L. Kraus  
Edward W. Yee  
Albert L. Ferro\*  
Donald R. Banowitz  
Peter A. Jackman  
Molly A. McCall  
Teresa U. Medler  
Jeffrey S. Weaver  
Kendrick P. Patterson  
Vincent L. Capuano  
Albert J. Fasulo II\*  
Eldora Ellison Floyd  
Thomas C. Fiala  
Brian J. Del Buono  
Virgil Lee Beaston\*

Kimberly N. Reddick  
Theodore A. Wood  
Elizabeth J. Haanes  
Bruce E. Chalker  
Joseph S. Ostroff  
Frank R. Cottingham  
Christine M. Lhulier  
Rae Lynn Prengaman  
Jane Shershenovich\*  
Lawrence J. Carroll\*  
George S. Bardmesser  
Daniel A. Klein\*  
Rodney G. Maze  
Jason D. Eisenberg  
Michael D. Specht  
Andrea J. Kamage  
Tracy L. Muller\*  
Jon E. Wright\*

LuAnne M. Yuricek\*  
John J. Figueroa  
Ann E. Summerfield  
  
**Registered Patent Agents\***  
Karen R. Markowicz  
Nancy J. Leith  
Helene C. Carlson  
Gaby L. Longworth  
Matthew J. Dowd  
Aaron L. Schwartz  
Angelique G. Uy  
Mary B. Tung  
Katrina Y. Pei  
Bryan L. Skelton  
Robert A. Schwartzman  
Timothy A. Doyle  
Jennifer R. Mahalingappa

Teresa A. Colella  
Jeffrey S. Lundgren  
Victoria S. Rutherford  
Eric D. Hayes

**Of Counsel**  
Kenneth C. Bass III  
Lisa A. Dunner  
Evan R. Smith

\*Admitted only in Maryland  
\*Admitted only in Virginia  
\*Practice limited to  
Federal Agencies

May 27, 2003

**WRITER'S DIRECT NUMBER:**

(202) 772-8673

**INTERNET ADDRESS:**

JCOVERT@SKGF.COM

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

*Via Hand Carry  
to Group Art Unit 1626  
Examiner G. Shameem*

*Mail Stop Issue Fee*

Re: U.S. Utility Patent Application  
Appl. No. 09/814,123; Filed: March 22, 2001  
For: **Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use  
Thereof**  
Inventors: HOGENKAMP *et al.*  
Our Ref: 1861.1270001/JMC/THN

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Amendment Under 37 C.F.R. § 1.312;
2. One sheet of drawings (Figs. 1A-1D); and
3. One (1) return postcard.

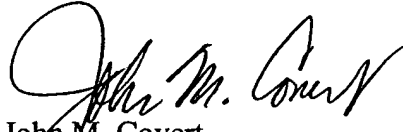
It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents  
May 27, 2003  
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read "John M. Covert", is written over the printed name.

John M. Covert  
Attorney for Applicants  
Registration No. 38,759

Enclosures

SKGF\_DC1:137220.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

HOGENKAMP *et al.*

Appl. No. 09/814,123

Filed: March 22, 2001

For: Aryl Substituted Pyrazoles,  
Triazoles and Tetrazoles, and the Use  
Thereof

Confirmation No. 2060

Art Unit: 1626

Examiner: Shameem, G.

Atty. Docket: 1861.1270001/JMC/THN

**Amendment Under 37 C.F.R. § 1.312**

Commissioner for Patents  
Washington, D.C. 20231

*Mail Stop Issue Fee*

Sir:

In reply to the Examiner's request during a telephone conference of May 22, 2003, submitted herewith is an Amendment Under 37 C.F.R. § 1.312. As payment of the issue fee has not yet been made or is filed herewith, Applicants respectfully submit that filing under 37 C.F.R. § 1.312 is proper (M.P.E.P. § 714.16). This Amendment is provided in the following format:

- (A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;
- (B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.111 and MPEP 714; and
- (C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees

for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

### ***Amendment***

#### ***In the Application:***

Please insert the attached sheet of FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D at the end of the application.

#### ***In the Specification:***

Please insert the following heading after paragraph [0019] and above the heading "DETAILED DESCRIPTION OF THE INVENTION":

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

Please insert under the heading "BRIEF DESCRIPTION OF THE DRAWINGS" the following new paragraph:

FIGS. 1A, 1B, 1C, and 1C are voltage pulse protocols used to assess the potency and kinetics of inhibition of the Na<sup>+</sup> channels by the compounds as follows: FIG. 1A: IV-curves, FIG. 1C: steady-state inactivation, FIG. 1B: repriming kinetics, and FIG. 1D: time course of binding.

Please substitute paragraph [0104] at page 20 with the following paragraph:

The following voltage pulse protocols A, B, C, and D are used to assess the potency and kinetics of inhibition of the Na<sup>+</sup> channels by the compounds (FIGS. 1A-1D). Current-voltage relationship (IV-curve), protocol A, is used to report the voltage at which the maximal inward Na<sup>+</sup> current is achieved. This voltage is used throughout the experiment as testing voltage, V<sub>t</sub>. The steady-state inactivation (or, availability) curve, protocol C, is used to get the voltage at which almost complete

( $\geq 95\%$ ) inactivation of  $\text{Na}^+$  channels occurs; it serves as voltage for conditioning prepulse,  $V_c$ , throughout the experiment. Protocol **B** reports how fast the channels recover from inactivation at hyperpolarized voltages. This permits us to set up the duration of the hyperpolarization gap which is used in measurement of the kinetics of binding of compounds to inactivated  $\text{Na}^+$  channels (protocol **D**). Channel repriming under control conditions is fast ( $\geq 90\%$  recovery during first 5-10 ms). If a drug substantially retards the repriming process, then it becomes possible (protocol **D**) to accurately measure the kinetics of binding of the inhibitor to inactivated channels as well as the steady-state affinity ( $k_+$  and  $K_i$ ). To estimate  $k_+$  values, the reduction in peak currents in successive trials with varying pre-pulse duration is plotted as a function of pre-pulse duration and the time constant ( $\tau$ ) measured by mono-exponential fit. A plot of  $1/\tau$  as a function of antagonist concentration then allows calculating of the macroscopic binding rates of the antagonists. To determine  $K_i$  values the partial inhibition curves measured by fractional responses in steady-state are fitted with the logistic equation:

$$I/I_{\text{control}} = 1/(1 + ([\text{antagonist}]/K_i)^p), \quad \text{Eq. 2}$$

where  $I_{\text{control}}$  is the maximal  $\text{Na}^+$  current in the absence of antagonist,  $[\text{antagonist}]$  is the drug concentration,  $K_i$  is the concentration of antagonist that produces half maximal inhibition, and  $p$  is the slope factor.

### ***Remarks***

None of the amendments add new matter. The amendments merely correct a formal matter without changing the scope of the claims.

The Examiner requested on May 22, 2003, that Fig. 1 on page 20 be deleted and, *in lieu* thereof, inserted at the end of the application. Further, the Examiner requested a new paragraph be added, entitled "Brief Description of the Drawings".

Accordingly, the application has been amended by inserting a sheet of FIGS. 1A-1D at the end of the application that correspond to the original Fig. 1. The symbols A, B, D, and D in the drawing have been amended to read FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D, respectively. No new matter has been added by this amendment.

The specification has been amended by inserting a new paragraph entitled "BRIEF DESCRIPTION OF THE DRAWINGS" after paragraph [0019]. This new paragraph includes the first sentence of paragraph [0104] and the figure text below the Fig. 1. The symbols A, B, D, and D of the figure text have been amended to read FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D, respectively. No new matter has been added by this amendment.

The specification has been also amended by deleting Fig. 1 and the figure text from paragraph [0104] at page 20. Further, paragraph [0104] has been amended by adding --A, B, C, and D-- after "protocols" at line 1 of the paragraph and replacing "(Fig. 1)" with --(FIGS. 1A-1D)--. No new matter has been added by these amendments.

Support for the amendments can be found in the original specification as filed.

Accordingly, Applicants request that these amendments be entered.

Reconsideration of this application and entry of the above Amendment is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



John M. Covert  
Attorney for Applicants  
Registration No. 38,759

Date: May 27, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

**Version with markings to show changes made**

***In the Application:***

The attached sheet of FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D has been inserted at the end of the application.

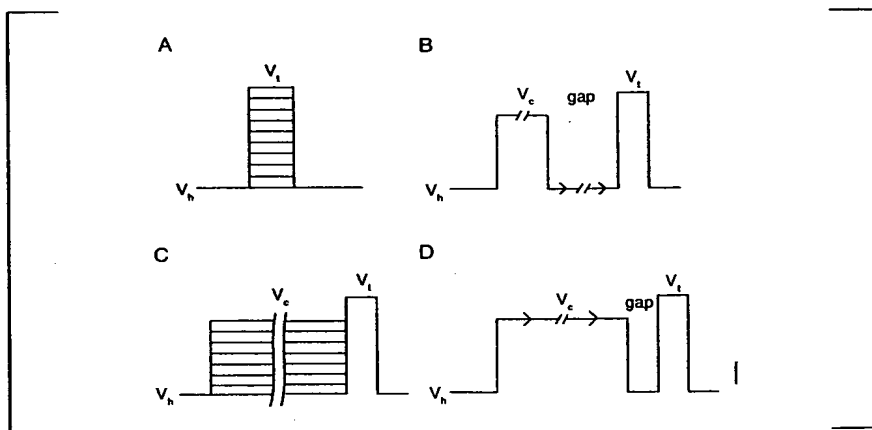
***In the Specification:***

A heading has been inserted after paragraph [0019] and above the heading "DETAILED DESCRIPTION OF THE INVENTION".

A new paragraph has been inserted under the heading "BRIEF DESCRIPTION OF THE DRAWINGS".

Paragraph [0104] at page 20 has been amended as follows:

The following voltage pulse protocols A, B, C, and D are used to assess the potency and kinetics of inhibition of the Na<sup>+</sup> channels by the compounds ([Fig. 1] FIGS. 1A-1D).





[Figure 1. Voltage pulse protocols. A. IV-curves. C. Steady-state inactivation. B. Repriming kinetics. D. Time course of binding.]

Current-voltage relationship (IV-curve), protocol A, is used to report the voltage at which the maximal inward Na<sup>+</sup> current is achieved. This voltage is used throughout the experiment as testing voltage, V<sub>t</sub>. The steady-state inactivation (or, availability) curve, protocol C, is used to get the voltage at which almost complete (≥95%) inactivation of Na<sup>+</sup> channels occurs; it serves as voltage for conditioning prepulse, V<sub>c</sub>, throughout the experiment. Protocol B reports how fast the channels recover from inactivation at hyperpolarized voltages. This permits us to set up the duration of the hyperpolarization gap which is used in measurement of the kinetics of binding of compounds to inactivated Na<sup>+</sup> channels (protocol D). Channel repriming under control conditions is fast (≥90% recovery during first 5-10 ms). If a drug substantially retards the repriming process, then it becomes possible (protocol D) to accurately measure the kinetics of binding of the inhibitor to inactivated channels as well as the steady-state affinity (k<sub>+</sub> and K<sub>i</sub>). To estimate k<sub>+</sub> values, the reduction in peak currents in successive trials with varying pre-pulse duration is plotted as a function of pre-pulse duration and the time constant (τ) measured by mono-exponential fit. A plot of 1/τ as a function of antagonist concentration then allows calculating of the macroscopic binding rates of the antagonists. To determine K<sub>i</sub> values the partial inhibition curves measured by fractional responses in steady-state are fitted with the logistic equation:

$$I/I_{\text{control}} = 1/(1 + ([\text{antagonist}]/K_i)^p), \quad \text{Eq. 2}$$

where I<sub>control</sub> is the maximal Na<sup>+</sup> current in the absence of antagonist, [antagonist] is the drug concentration, K<sub>i</sub> is the concentration of antagonist that produces half maximal inhibition, and p is the slope factor.

FIG. 1A

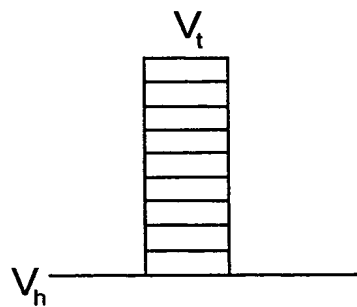


FIG. 1B

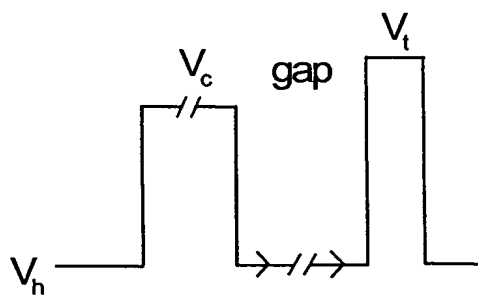


FIG. 1C

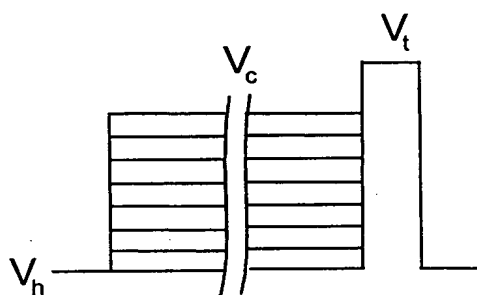
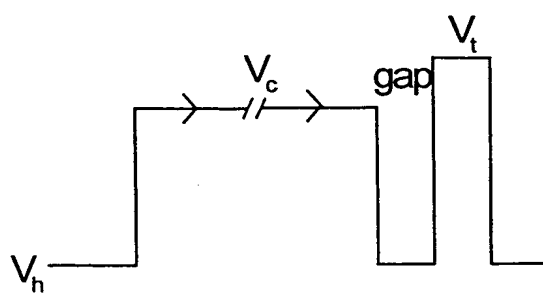


FIG. 1D



**Applicants:** Hogenkamp *et al.*  
**Application No.:** 09/814,123  
**Filed:** March 22, 2001  
**For:** Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use Thereof

**Due Date:** June 13, 2003  
**Art Unit:** 1626  
**Examiner:** Shameem, G.  
**Docket:** 1861.1270001  
**Atty:** JMC/THN

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. SKGF Cover Letter;
2. Amendment Under 37 C.F.R. § 1.312;
3. One sheet of drawings (Figs. 1A-1D); and
4. One (1) return postcard.

May 27, 2003

*Via Hand Carry*  
*Group Art Unit 1626*  
*Examiner G. Shameem*

Please Date Stamp And Return To Our Courier

SKGF\_DC1:137223.1

**Applicants:** Hogenkamp *et al.*  
**Application No.:** 09/814,123  
**Filed:** March 22, 2001  
**For:** Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use Thereof

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*Via Hand Carry*  
*Group Art Unit 1626*  
*Examiner G. Shameem*

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